1. NAME OF THE MEDICINAL PRODUCT

V-OPTIC 0.25 %

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

'V-OPTIC 0.25%' w/v Eye Drops Solution contains timolol maleate equivalent to 0.25% w/v solution of timolol with preservative.

3. PHARMACEUTICAL FORM

Eye drops solution.

Clear, colourless to light yellow, sterile eye drops solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the reduction of elevated intraocular pressure may be used in patients with chronic open angle glaucoma, aphakic glaucoma, some patients with secondary glaucoma and patients with ocular hypertension.

4.2 Posology and method of administration

Recommended therapy is one drop in the affected eye twice a day.

If needed, 'V-OPTIC 0.25%' may be used with other agent(s) for lowering intra-ocular pressure. The use of two topical beta-adrenergic blocking agents is not recommended (see 4.4 'Special warnings and precautions for use').

Intra-ocular pressure should be reassessed approximately four weeks after starting treatment because response to 'V-OPTIC 0.25%' may take a few weeks to stabilise.

Provided that the intra-ocular pressure is maintained at satisfactory levels, many patients can then be placed on once-a-day therapy.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

Transfer from other agents
When another topical beta-blocking agent is being used, discontinue its use after a full day of therapy and start treatment the next day with one drop of 'V-OPTIC 0.25%' in each affected eye twice a day.

When transferring a patient from a single anti-glaucoma agent other than a topical beta-blocking agent, continue the agent and add one drop of 'V-OPTIC 0.25%' in each affected eye twice a day. On the following day, discontinue the previous agent completely, and continue with the 'V-OPTIC 0.25%'.

Use in the elderly: there has been wide experience with the use of timolol maleate in elderly patients. The dosage recommendations given above reflect the clinical data derived from this experience.

Paediatric Population:
Safety and effectiveness in pediatric patients have not been established.

4.3 Contraindications

Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease; sinus bradycardia, sick sinus syndrome, sino-atrial block, second- and third-degree atrioventricular block not controlled with pace-maker, overt cardiac failure, cardiogenic shock.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic agents, timolol is absorbed systemically. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see 4.2.

Cardiac disorders:
In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Cardiac failure should be adequately controlled before beginning therapy with 'V-OPTIC 0.25%'. Patients with a history of severe cardiac disease should be watched for signsof cardiac failure and have their pulse rates monitored.

Vascular disorders
Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders:

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

'V-OPTIC 0.25%' should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes
Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases
Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking agents
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoreceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessationof therapy involving beta-blockade should be gradual.

Choroidal detachment
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia
Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of epinephrine (adrenaline). The anaesthesiologist should be informed when the patient is receiving timolol.

'V-OPTIC 0.25%' has been generally well tolerated in glaucoma patients wearing conventionalhard contact lenses. 'V-OPTIC 0.25%' has not been studied in patients wearing lenses made with material other than polymethylmethacrylate (PMMA), which is used to makehard contact lenses.

'V-OPTIC 0.25%' contains Benzalkonium Chloride as a preservative which may be deposited insoft contact lenses; therefore 'V-OPTIC 0.25%' should not be used while wearing these lenses. The lenses should be removed before application of the drops and not reinserted earlier than 15 minutes after use.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. 'V-OPTIC 0.25%' has little or no effect on the pupil. When 'V-OPTIC 0.25%' is used to reduce elevated intra-ocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

Patients should be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose bottle (see 6.6 'Special precautions for disposal and other handling').

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Anaphylactic reactions
While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and, may be unresponsive to the usual dose of epinephrine (adrenaline) used to treat anaphylactic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with timolol maleate.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium-channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, rauwolfia alkaloids, parasympathomimetics, guanethidine.

Although 'V-OPTIC 0.25%' alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic beta-blockers and epinephrine (adrenaline) has been reported occasionally.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine,fluoxetine, paroxetine) and timolol.

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Oral calcium-channel antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.

The potential exists for hypotension, AV conduction disturbances and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium-channel blocker is added to the treatment regimen. The nature of any cardiovascular adverse effects tends to depend on the type of calcium-channel blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta-blocker.

Intravenous calcium channel blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

The concomitant use of beta-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data for the use of timolol maleate in pregnant women. 'V-OPTIC 0.25%' should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see 4.2.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If 'V-OPTIC 0.25%' is administered until delivery, the neonate should be carefully monitored during the first days of life.

Lactation

Timolol is detectable in human milk. A decision for breastfeeding mothers, either to stop taking 'V-OPTIC 0.25%' or stop nursing, should be based on the importance of the drug to the mother.

4.7 Effects on the ability to drive and use machines

Possible side effects such as dizziness, visual disturbances, refractive changes, diplopia, ptosis, frequent episodes of mild and transient blurred vision and fatigue may affect some patients' ability to drive or operate machinery.

4.8 Undesirable effects

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. The following adverse reactions have been reported with *ocular* administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed. Additional side effects have been reported in clinical experiences with *systemic* timolol maleate, and may be considered potential effects of ophthalmic timolol maleate. Also listed are adverse reactions seen within the class of ophthalmic beta- blockers and may potentially occur with 'V-OPTIC 0.25%'.

Eye disorders
ocular: signs and symptoms of ocular irritation, (e.g. burning, stinging, itching, tearing, redness), conjunctivitis, blepharitis, keratitis, dry eyes, decreased corneal sensitivity, blurred vision, corneal erosion. Visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis and choroidal detachment following filtration surgery (see 4.4 'Special warnings and precautions for use').

Ear and labyrinth disorders:
Ocular: tinnitus

Cardiac disorders
ocular: bradycardia, chest pain, arrhythmia, heart block, congestive heart failure, palpitations, cardiac arrest, atrioventricular block, cardiac failure, oedema; *systemic*: AV block (second - or third-degree), sino-atrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilation.

Vascular disorders:
ocular: claudication, hypotension, Raynaud's phenomenon, cold hands and feet.

Respiratory, thoracic and mediastinal disorders:
ocular: bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnoea, cough;
systemic: rales.

General disorders and administration site conditions:
ocular: asthenia, fatigue;
systemic: extremity pain, decreased exercise tolerance.

Skin and subcutaneous tissue disorders:
ocular: alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash;
systemic: sweating, exfoliative dermatitis.

Immune system disorders:
ocular: systemic lupus erythematosus, pruritus;
systemic: signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash, anaphylactic reaction.

Psychiatric disorders:
ocular: depression, insomnia, nightmares, memory loss;
systemic: diminished concentration, increased dreaming.

Nervous system disorders
ocular: syncope, cerebrovascular accident, cerebral ischemia, headache, dizziness, increase in signs and symptoms of myasthenia gravis, paraesthesia;
systemic: vertigo, local weakness.

Gastrointestinal disorders:
ocular: nausea, diarrhoea, dyspepsia, dry mouth, dysgeusia, abdominal pain, vomiting.

Reproductive system and breast disorders:
ocular: decreased libido, Peyronie's disease, sexual dysfunction such as impotence;
systemic: micturition difficulties.

Metabolism and nutrition disorders:
ocular: hypoglycaemia;
systemic: hyperglycaemia.

Musculoskeletal and connective tissue disorders:
ocular: myalgia;
systemic: arthralgia.

Blood and lymphatic system disorders:
systemic: non-thrombocytopenic purpura.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

If overdosage occurs, the following measures should be considered:

1. Gastric lavage, if ingested. Studies have shown that timolol does not dialyse readily.

2. Symptomatic bradycardia: atropine sulphate, 0.25 to 2 mg intravenously, should be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases, the use of a cardiac pacemaker may be considered.

3. Hypotension: a sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be useful.

4. Bronchospasm: isoprenaline hydrochloride should be used. Additional therapy with aminophylline may be considered.

5. Acute cardiac failure: conventional therapy with digitalis, diuretics, and oxygen should be instituted immediately. In refractory cases, the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon, which has been reported useful.

6. Heart block (second- or third-degree): isoprenaline hydrochloride or a pacemaker should be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic activity. Timolol maleate combines reversibly with the beta-adrenergic receptor, and this inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulationof the beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist which will restore the usual biological response.

Unlike miotics, 'V-OPTIC 0.25%' reduces IOP with little or no effect on accommodation or pupil size. In patients with cataracts, the inability to see around lenticular opacities when the pupil is constricted is avoided. When changing patients from miotics to 'V-OPTIC 0.25%' a refraction might be necessary when the effects of the miotic have passed.
Diminished response after prolonged therapy with timolol maleate has been reported in some patients.

5.2 Pharmacokinetic properties

The onset of reduction in intra-ocular pressure can be detected within one-half hour after a single dose. The maximum effect occurs in one or two hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose.

5.3 Preclinical safety data

No adverse ocular effects were observed in rabbits and dogs administered timolol maleate topically in studies lasting one and two years, respectively. The oral LD_{50} of the drug is 1,190 and 900 mg/kg in female mice and female rats, respectively.
Carcinogenesis, mutagenesis, impairment of fertility
In a two-year oral study of timolol maleate in rats there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal phaeochromocytomas in male rats administered 300 mg/kg/day (300 times the maximum recommended human oral

dose). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose.

In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day (500 times the maximum recommended human dose), but not at 5 or 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to uterus and lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant ($p \leq 0.05$) elevations of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose-response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Disodium Hydrogen Phosphate Heptahydrate
Sodium Dihydrogen Phosphate $2H_2O$
Benzalkonium Chloride, Disodium Edetate
Sodium Hydroxide and/or Hydrochloric Acid
Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Discard 'V-OPTIC 0.25%' Eye Drops Solution 30 days after first opening the bottle.

6.4 Special precautions for storage

Store in a dry place, below 25°C.

6.5 Nature and contents of container

V-Optic 0.25% is supplied in a 5 ml LDPE bottle with a LDPE/HDPE dropper/cap.

6.6 Special precautions for disposal and other handling

Patients should be instructed to avoid allowing the tip of the bottle to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

7. REGISTRATION HOLDER

VITAMED PHARMACEUTICAL INDUSTRIES LTD.,
6 HATAHANA ST., P.O.B 114, BINYAMINA 3055002, ISRAEL

8. REGISTRATION NUMBER(S)

069-80-28592-00

9. MANUFACTURER

VITAMED PHARMACEUTICAL INDUSTRIES LTD.,
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